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(54) Title: PHARMACEUTICAL COMBINATION OF IBUPROFEN–LYSINE AND DOMPERIDONE FOR TREATING MIGRAINE

(57) Abstract

The present invention relates to a combination of ibuprofen lysine and domperidone for treating and/or preventing migraine, migraine–associated nausea and vomiting and headache with nausea following overindulgence.

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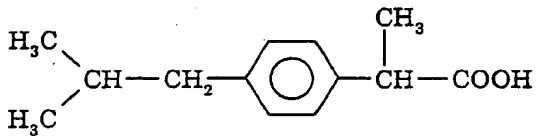
PHARMACEUTICAL COMBINATION OF IBUPROFEN-LYSINE AND DOMPERIDONE FOR TREATING MIGRAINE

The present invention relates to a pharmaceutical composition comprising a combination of active ingredients. More particularly, the invention concerns a pharmaceutical formulation comprising ibuprofen lysinate in combination with domperidone or a salt thereof, for use in the control of migraine, and in particular migraine-associated nausea and vomiting, and of headache with nausea following overindulgence.

Migraine is a recurrent, often familial, symptom complex of periodic attacks of vascular headache, which is frequently associated with nausea and vomiting. Migraine affects approximately 17% of adult women and 6% of adult men (Stewart *et al.*, *Neurology*, 1994, 44 (suppl. 4), 517-523).

Ibuprofen, or (±)-2-(*p*-isobutylphenyl)propionic acid, is a well-known non-steroidal anti-inflammatory drug (NSAID) of the formula



The compound is widely prescribed for its analgesic and anti-pyretic activity. It is also available as a low dose over-the-counter product to be used orally for the treatment of minor aches and pains, and as a topically applied gel for the treatment of muscular sprains and strains.

The lysine salt of ibuprofen has been developed in order to confer water solubility upon the compound, primarily to assist in the development of an injectable form of ibuprofen. Thus, for example, UK Patent Specification No. 1,471,910 (published 27th April 1977) describes the lysine salt of ibuprofen and its formulation as injectable solutions, tabloids, freeze-dried in vials on a mannitol support, ampoules, capsules, suppositories and ointments for local applications.

Clinical experience suggests that, amongst all the available modes of administration, patients find that orally administered medicaments are the simplest to use. However, the efficacy of drugs given orally to relieve migraine attacks is not always reliable as gastrointestinal motility is inhibited even in the earliest stages of an attack, and there is always a risk of nausea during the attack culminating in vomiting.

It has now been found that these disadvantages can be overcome by the co-administration of a ibuprofen lysinate in conjunction with domperidone or a pharmaceutically acceptable salt thereof, the resulting combined formulation displaying beneficial effects in controlling migraine-associated nausea and vomiting and in headache and nausea associated with overindulgence.

Domperidone has an antinauseant effect through an action at the chemoreceptor trigger zone. It also has a gastric prokinetic effect through an action on gut dopaminergic receptors. Gastric stasis is a feature of migraine attacks and can also contribute to nausea experienced after an excess of alcohol consumption. It is also possible that domperidone will increase the absorption of the ibuprofen lysine through counteracting gastric stasis.

Ibuprofen lysinate provides rapid absorption of racemic ibuprofen because the lysine salt is very soluble. Thus this compound is particularly well suited to treatment of headache in migraine and overindulgence where drug absorption may be compromised.

Despite the above-mentioned advantageous properties of the compounds used in the present invention, their combination has been nowhere suggested in the prior art. Further the combination is surprisingly effective in providing a fast-acting anti-nauseant medication for the treatment of migraine-associated nausea and vomiting and of headache with nausea following overindulgence.

Furthermore, as both compounds are well known the combination has the advantage of being unexpectedly efficacious and safe for self

medication without medical supervision. This overcomes the long standing problem of the lack of effective self administered migraine and overindulgence medications which usually consist of an analgesic alone and thus suffer from the above-mentioned drawbacks.

The present invention accordingly provides a method for the treatment and/or prevention of migraine which comprises administering to a patient in need of such treatment, simultaneously, separately or sequentially, an effective amount of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for the treatment and/or prevention of migraine-associated nausea and vomiting or of headache with nausea following overindulgence, which comprises administering to a patient in need of such treatment, simultaneously, separately or sequentially, an effective amount of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of migraine.

The present invention further provides the use of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of migraine-associated nausea and vomiting or of headache with nausea following overindulgence.

In another aspect, the present invention provides a pharmaceutical composition comprising ibuprofen lysinate in association with domperidone or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a product comprising ibuprofen lysinate and domperidone or a pharmaceutically

acceptable salt thereof as a combined preparation for simultaneous, separate or sequential use in the treatment and/or prevention of migraine.

In a yet further aspect, the present invention provides a product comprising ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof as a combined preparation for simultaneous, separate or sequential use in the treatment and/or prevention of migraine-associated nausea and vomiting or of headache with nausea following overindulgence.

In the normal practice of the invention, ibuprofen lysinate and domperidone or its pharmaceutically acceptable salt will usually be administered to a patient within a reasonable period of time, which will typically be up to about one hour apart. The compounds may be in the same pharmaceutical carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers and administered simultaneously, by mixing the materials just prior to administration. They may alternatively be in different dosage forms which can be taken simultaneously, or adminstered sequentially.

As is evident from its chemical name, ibuprofen is a racemic mixture. The active enantiomer of ibuprofen is the *S*(+) enantiomer. Whilst the present invention refers in general to the racemate it will be appreciated that the *S*(+) enantiomer of ibuprofen in the form of its lysine salt may be used in the same manner. A particularly convenient method for the formation and resolution of (*S*)-ibuprofen-(*S*)-lysine is described in US Patent No. 4,994,604 (published 19th February 1991).

It will also be appreciated that the lysine may exist in its racemic form or as single enantiomers. Whilst the present invention refers in general to the racemate it will be appreciated that either enantiomer, such as the naturally occurring *S*(+) enantiomer (i.e. the *laevo* (L) form), may be used in the same manner.

The pharmaceutical composition according to the present invention may conveniently be adapted for administration orally, rectally or

parenterally. For oral administration, the formulation may be presented in the form of tablets, pills, capsules, powders or granules; for parenteral administration, sterile parenteral solutions or suspensions may conveniently be utilised; and for rectal administration, the formulation may conveniently be in the form of suppositories. Suitably, the pharmaceutical compositions in accordance with the invention may be presented in the form of a kit of parts adapted for simultaneous, separate or sequential administration.

The compositions may be formulated by conventional methods well known in the pharmaceutical art, for example as described in *Remington: The Science and Practice of Pharmacy*, Mack Publishing Company, 19th Edition, 1995.

For administration in combination, the ibuprofen lysinate and the domperidone or its pharmaceutically acceptable salt may be presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the molar ratio of ibuprofen lysinate to domperidone or its pharmaceutically acceptable salt will suitably be approximately 1 to 1. Preferably, this ratio will be between 0.001 to 1 and 1000 to 1, and especially from 0.01:1 to 100:1.

For co-administration with domperidone or a pharmaceutically acceptable salt thereof in the treatment of migraine, and in particular migraine-associated nausea and vomiting or overindulgence, ibuprofen lysinate may suitably be administered at a daily dosage of about 0.001 to 250 mg/kg, typically about 0.005 to 100 mg/kg, more particularly about 0.01 to 50 mg/kg, and especially about 0.05 to 10 mg/kg. For co-administration with ibuprofen lysinate in the treatment of migraine, and in particular migraine-associated nausea and vomiting or overindulgence, domperidone or a pharmaceutically acceptable salt thereof may suitably be administered at a daily dosage of about 0.001 to 250 mg/kg, typically about 0.005 to 100 mg/kg, more particularly about 0.01 to 50 mg/kg and

especially about 0.05 to 10 mg/kg. The active ingredients will typically be co-administered on a regimen of 1 to 4 times per day.

A sample treatment regime based upon a tablet containing 10 mg of domperidone and 342 mg of ibuprofen lysinate (equivalent to 200 mg of ibuprofen) is as follows:

for migraine - two tablets at the beginning of an attack with a dosage repeat after four hours if necessary up to a maximum of four dosages in twenty-four hours;

for overindulgence - one or two tablets at the beginning of an attack repeated after four hours if necessary up to a maximum of eight tablets in one day.

The following non-limiting Example serves to illustrate the present invention.

EXAMPLE 1

1,000 tablets were prepared as follows:

Blending:

Ibuprofen lysinate, compacted and Domperidone are pre-blended by hand in a pan.

Polyvidon K 29/32 and microcrystalline cellulose are added and hand-blended.

Magnesium stearate is then added and hand-blended.

The mix is finally blended in a 3,5 l-cubemixer for 30 minutes to obtain the final mix.

Compressing:

The final mix is compressed to obtain round, flat tablets of 13 mm diameter and 409 mg weight, using a Korsch KO excenter tablet press.

Formula per tablet:

Ibuprofen lysinate, compacted	342.0 mg
Domperidone	10.0 mg
Polyvidon K 29/32	17.0 mg
Microcrystalline Cellulose	36.0 mg
Magnesium Stearate	4.0 mg
	409.0 mg

The microcrystalline cellulose may be Avicel PH102. The magnesium stearate is generally from a vegetal source. In addition to the above ingredients about 4mg talc may be added to the mixture. Lactose fast flow may also be added.

The tablets may be supplied with a film coating comprising hypromellose, hydroxypropylcellulose, titanium dioxide and water.

CLAIMS:

1. A pharmaceutical composition comprising ibuprofen lysinate in association with domperidone or a pharmaceutically acceptable salt thereof.

2. A product comprising ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof as a combined preparation for simultaneous, separate or sequential administration.

3. The use of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of migraine.

4. The use of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of migraine-associated nausea and vomiting or of headache with nausea following overindulgence.

5. A method for the treatment and/or prevention of migraine which comprises administering to a patient in need of such treatment simultaneously, separately or sequentially, an effective amount of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof.

6. A method for the treatment and/or prevention of migraine-associated nausea and vomiting or of headache with nausea following overindulgence, which comprises administering to a patient in need of such treatment, simultaneously, separately or sequentially, an effective

amount of a combination of ibuprofen lysinate and domperidone or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intes onal Application No
PCT/GB 99/03398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 34612 A (THE BOOTS COMPANY PLC) 13 August 1998 (1998-08-13) claims 1,4 page 1, line 9 -page 2, line 10 page 3, line 9-29 page 6, line 8-12	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2000	10/03/2000

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information on patent family members

Inte onal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834612 A	13-08-1998	AU 6295598 A	26-08-1998
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		GB 2331926 A	09-06-1999
		NO 993784 A	22-09-1999
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